

Accepted Manuscript

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PII: S0091-6749(19)30483-X

DOI: <https://doi.org/10.1016/j.jaci.2019.04.002>

Reference: YMAI 13961

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 13 March 2019

Revised Date: 4 April 2019

Accepted Date: 5 April 2019

Please cite this article as: Renz H, DNA methylation and a biomarker panel to predict asthma development, *Journal of Allergy and Clinical Immunology* (2019), doi: <https://doi.org/10.1016/j.jaci.2019.04.002>.

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Editorial: collaboration JACI and The Lancet

Respiratory Medicine (LRM):

DNA methylation and a biomarker panel to predict asthma development

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Funding

Harald Renz is funded by the Universities Giessen Marburg Lung Center and the German Center for Lung Disease (DZL German Lung Center, no. 82DZL00502) for UGMLC

Disclosure Statement

Dr. Renz declares that he has no relevant conflicts of interest.

Keywords

DNA methylation; biomarker panel; asthma

With the advent of precision medicine, systems biology and the availability of targeted therapeutic approaches (e.g. using monoclonal antibodies), the need arises regarding the availability of appropriate biomarkers to stratify patient populations. Not only in this aspect is the field of allergy and asthma research rapidly advancing and actually represents the prime example for this new chapter in patient care of allergic, asthmatic, and immunologically dysfunctional patients.

A recent article in *Lancet Respiratory Medicine*¹ illustrates elegantly this advancement in the field. Since it is now well established that a single biomarker will not be able to stratify allergic and atopic asthmatic patients (including children) accurately, the search of appropriate biomarker panels is currently ongoing. Another challenge is the availability of appropriate biomaterials in order to assess such potential biomarkers in a less or even non-invasive fashion, but simultaneously reflecting the local inflammatory pattern in lung and airways.

With regard to systems biology, biomarker assessment may include the level of genomics (DNA), the transcriptomic level of regulation or the epigenetic level of regulation (e.g. histone modifications, DNA methylation, and others) (mRNA) or the metabolomic level (e.g. proteins, lipids, carbohydrate metabolites).

The paper by Forno et al.¹ advances in this regard in several ways: (i) they used easily accessible nasal epithelium as the biomaterial of choice; (ii) they analyzed the nasal methylome on the epigenetic level in these cells in a state-of-the-art comprehensive fashion; (iii) based on this comprehensive analysis, they defined a panel of the top 30 CpG islets (which are the prime site for introduction of CH3 methylation), and (iv) validated this panel in two further cohorts as a replicate (analysis was performed in a total of three cohorts).

In essence, they performed a genome-wide study of DNA methylation on nasal epithelium in 483 school-aged children in Puerto Rico to identify the signature associated with atopy or

atopic asthma. Using this approach of classification models of atopy based on nasal methylation, they observed an accuracy of 85-88% Area Under the Curve (AUC) 0.93-0.94 in the original Puerto Rico cohort); in the Yang et al. cohort ², they reached an accuracy of 82% together with AUC 0.91-0.92, and in the PIAMA ³ cohort an accuracy of 0.73 with an AUC of 0.73-0.79. Similar results were obtained for the prediction of atopic asthma.

It is remarkable that the unbiased epigenetic methylome approach resulted in the selection of this 30-CpG panel predicting relatively accurately atopy or asthma in children. Let us take a further look at the genes exhibiting this hyper- or hypomethylation. Several of these genes are implicated in epithelial barrier processes such as CDH26 (cadherin family protein), CDHR3 (implicated in rhinovirus infection and asthma exacerbation)^{4,5}; and others. Other genes involved include NTRK1, previously linked to neurogenic inflammation ⁶, PCSK6 (involved in activation of NFkB) ⁷, NFBX7 (associated with decreased inhaled corticosteroid responses) ⁸, GFK5 (involved in beta-2 adrenergic receptor responses) Wang et al. ⁹ and others.

Many of the genes identified on the level of epigenetic regulation have not been previously implied in studies analyzing the genomic level. Furthermore, these epigenetic changes are different from epigenetic changes observed in the peripheral blood of asthmatic patients ¹⁰.

Although the study has certain limitations such as its cross-sectional structure and the absence of non-atopic asthmatic individuals in this cohort (while they included a cohort of no atopy); the result clearly indicates that epigenetic regulation in the nasal epithelium compartment seems to be closely related to atopy and asthma development. However, whether these epigenetic marks precede the development of these conditions or are more directly related to the disease as such, remains to be investigated in further studies. Also, since many of the implied genes are not known for their respective function in asthma, further mechanistic studies are certainly required. In addition, the hierarchy of the involved genes

and the network of this dysregulation of the epigenetic level need to be further analyzed and validated on the functional level as well. This study opens a new approach in biomarker development, assessment, and validation and we are eager to learn more about the underlying mechanistic dysregulation of airway epithelium with regard to the development of allergies and asthma.

Further prospective studies are needed to investigate whether these panels could be used for early predication of asthma and for the assessment of therapeutic responses in asthmatic children. Also, it needs to be investigated whether this approach is limited to pediatric asthma or can be extended to adult asthma as well.

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